Appl. No. 10/694,641
Amdt. dated June 13, 2006
Reply to Office Action of December 29, 2005

## REMARKS/ARGUMENTS

### I. Status of the Claims

Claims 14-23 and 26-45 are pending. Claims 19, 20, 35 and 36 are withdrawn pursuant to the restriction required in the Office Action and claims 42-45 have been added.

### II. The Present Amendment

No new matter has been added by the present amendments.

Claims 14 and 30 have been amended to recite that that the inhibitor of sEH inhibits by 50 % the activity of the enzyme in hydrolyzing epoxides at a concentration of less than about 500 μM (that is, that it has an $IC_{50}$ of less than about 500 μM). The recitation is supported throughout the specification, including page 3, lines 10-12. That the enzyme activity referred to is epoxide hydrolysis is also supported throughout the specification, including the fact that the exemplar sEH inhibitor DCU was directly tested for its effect on inhibiting the hydrolysis of epoxyeicosatrienoic acids (EETs). See, specification at pages 32-33, paragraph 0074. New claims 42 and 43 are supported by, *inter alia*, the disclosure of U.S. Application No. 09/252,148, now U.S. Patent No. 6,150,415, at, e.g., column 7, lines 20-33, showing that compound 2 (DCU) inhibited sEH activity by 99.3 % ± 0.8 at 100 μM. The passage characterizes this degree of inhibition as inhibiting totally the activity of the enzyme. The present application claims priority to the '148 application, which is legally therefore part of the present disclosure. See, specification, page 1, paragraph 1. (For the sake of good order, Applicants note that the enzyme previously referred to as "cytosolic EH" is the enzyme now referred to in the art as "soluble epoxide hydrolase," or "sEH." See, e.g., U.S. Patent No. 6,890,925, column 1, at lines 30-35.) New claims 44 and 45 are supported throughout the specification, including pages 27-8, paragraph 0060.

## III. The Office Action

The Office Action dated December 29, 2005 (the "Action") rejects the claims on several grounds. Applicants traverse. The rejections will be addressed separately below.

### A. Affirmation of Restriction

Applicants hereby affirm the election made by phone on December 7, 2005 to prosecute the invention of Group I and the species set forth in the Action at page 3, paragraph 3.

### B. Rejection for alleged lack of written description

Claims 14, 21-23, 26-30, and 37-41 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being described in such a way as to reasonably convey that at the time of the invention, the applicants had possession of the invention. According to the Action, the specification discloses three compounds that are examples of inhibitors of the enzyme known as soluble epoxide hydrolase (hereafter "sEH") and tested for their efficacy in decreasing blood pressure in rats. Action, at page 4. The Action asserts that while there is written description for these three compounds, the claims are directed to any inhibitor of sEH, "necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. . . . The specification provides insufficient written description to support the genus encompassed by the claim[s]." Action, at page 5. The Action further asserts that with the three compounds tested, "the skilled artisan cannot envision which 'soluble epoxide hydrolase inhibitor' would have similar activity as the tested compounds." Action, at page 5. Applicants traverse.

With respect, the rejection is premised on a fundamental confusion between the studies underlying the invention and the written description regarding inhibitors of sEH. Turning first to the studies underlying the invention, the specification reports that there was a difference in hydrolysis of EETs (epoxide substrates which sEH converts into diols) in the kidneys of spontaneously hypertensive rats ("SHR") compared to those of normotensive WKY rats, and that this difference in hydrolysis was correlated with the finding that the microsomes of the hypertensive rats had sEH protein levels 6- to 90- times higher than those of the normotensive WKY rats. *See*, specification at page 31, paragraph 0071. The studies in the specification

further demonstrate that the strong inhibitors of sEH tested had a dramatic effect on blood pressure in the hypertensive rats, (specification, at page 33, paragraph 0076), while a weak sEH inhibitor had no effect on blood pressure. *Id.*, at lines 30-33. Thus, the specification contains studies leading the person of skill to correlate the anti-hypertensive effect of the agents tested to their effect on inhibiting sEH. Specification, at page 33, line 34, to page 34, line 2.

We turn now to the written description of inhibitors of sEH. Contrary to the assumption underlying the rejection, no fewer than 11 pages of the specification are devoted to setting forth structures and activity data for compounds of Formula I. In fact, the specification sets forth data for no fewer than 132 compounds of Formula 1, all of which were tested and shown to strongly inhibit sEH, as evidenced by the fact they have $IC_{50}$s for human sEH in the low micromolar range. *See*, Table 1, at pages 3-13. Thus, contrary to the rejection's premise, the specification contains written description for a large number of species within the claimed genus. Given the results on blood pressure shown by the exemplar compounds in the studies noted in the specification, all of these additional compounds are also expected to be active in reducing blood pressure. The rejection fails even to acknowledge the presence of this written description and, since it does not even acknowledge the presence of this description, of course neither argues nor shows that this description of over 130 species within the genus somehow would not support the claims to the genus as a whole.

The rejection is thus based on a false premise. There is ample written description supporting the genus. Reconsideration and withdrawal of the rejection is respectfully requested.

**C. Rejection for alleged lack of enablement**

Claims 14-18, 21-23, 26-34, and 37-41 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled. According to the Action, the specification is enabled for the three specific inhibitors of sEH set forth in the working examples, but not for any inhibitor of sEH, such as those in which the Z in formula 1 is sulfur, the W is phosphorus or sulfur, and Y is oxygen or sulfur. Action, at page 6. Applicants traverse.

The Action correctly notes at pages 6-7 the factors set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The rejection is, however, premised in part on the incorrect

assertion in the Action, at page 8, that "very limited numbers of the compounds are set forth as working examples in the instant specification." As pointed out in the preceding section, the specification actually sets forth at pages 3-13 the structures of over 130 compounds that strongly inhibit sEH activity. The Action's analysis of the *Wands* factors is therefore premised on an incorrect understanding of the support in the specification. Since the Action's understanding of the specification's teachings is seriously flawed, the weighting of the *Wands* factors alleged to support the rejection is correspondingly incorrect. Applicants respectfully submit that the rejection must be reconsidered, and upon reconsideration, withdrawn on this basis alone.

For extra measure, however, Applicants also observe that the specification further sets forth, at pages 33-34, studies indicating the effect of three different, exemplar sEH inhibitors on blood pressure *in vivo*, indicating that the effect on blood pressure is due to their shared property of inhibiting the activity of sEH. The Action sets forth no evidence or argument why the almost 130 other sEH inhibitors reported at pages 3-13 of the specification would not have the same pharmacological activity as the exemplar compounds tested. The rejection therefore not only seriously understates the support set forth in the specification, but also arrives at an incorrect conclusion.

Had the Action not overlooked the presence of Table 1, the information it presents on the 130 compounds set forth thereon, and the further teachings of the specification, it could not have made the rejection on the basis that the specification does not enable the various substitutions recited in Formula I. For example, the rejection argues that there is no enablement for embodiments in which Y (and, by extension, X) is oxygen. In fact, however, the first 15 compounds set forth in Table 1 are strong inhibitors of sEH that have oxygen at either position X or Y. Similarly, the rejection incorrectly states that there is no enablement for compounds in which Z is sulfur. The Examiner will recognize that a urea in which a sulfur is substituted for the oxygen is a thiourea. The specification teaches that thioureas are prodrugs which are metabolized to yield the active parent structure. It specifically notes that the thiourea "dicyclohexyl thio urea can be oxidized to dicyclohexylcarbodiimide which . . . will form active dicyclohexylurea." Specification, at page 22, lines 6-8, and discloses the use of other prodrugs at page 22, lines 11-28. Once again, the rejection is founded on a fundamental misperception of the

enablement provided in the specification. *See also*, U.S. Patent No. 6,150,415, at column 6, Table 2, compounds 11 and 12.

The Action further errs in stating that the specification does not present any "competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instantly claimed compounds." Action, at page 7. As an initial matter, it is respectfully noted that assays for determining epoxide hydrolase activity were known in the art well prior to the present invention, and it was therefore not necessary to teach them in the present specification. The well established rule is that "the specification not need teach, and preferably omits, that which is well known in the art." See, e.g., *In re Buchner*, 18 USPQ2nd 1331, 1332 (Fed. Cir. 1991).

Applicants respectfully call the Examiner's attention, however, to the fact that a number of assays known in the art are referenced in the specification, at page 23, paragraph 0041. These assays were incorporated by reference into the specification at page 35, paragraph 0079. They are, therefore, legally part of the specification's teachings. The assay taught in the 1993 Zeldin et al. reference cited at page 23, lines 26-27, was in fact used in the studies underlying the present invention to determine the hydrolysis of EETs in rat renal fractions, as noted in the specification at page 29, paragraph 0065. The Action sets forth no evidence or rationale as to why these assays would not permit the practitioner to demonstrate sEH inhibitory activity, or why this sEH inhibitory activity would not be correlated with pharmacological activity in reducing blood pressure. The rejection therefore again understates the support set forth in the specification and therefore arrives at an incorrect weighting of the *Wands* factors.

Applicants respectfully remind the Examiner that the claims are permitted to encompass non-working embodiments, so long as the specification contains teachings by which the practitioner can readily determine whether any particular embodiment would work. In the present case, the assays noted above and known in the art permit the practitioner to readily determine whether any particular compound within those encompassed by Formula I inhibits sEH and therefore will have the effect of reducing blood pressure.

The Action further fails to note that the relative skill of persons in this art is very high. Typically, the persons working in this area would be medicinal chemists or persons with a

Ph.D. in a related field. As the Examiner is aware, the amount of guidance needed to be provided in a specification is inversely related to the level of skill of the practitioner in the relevant art. The high degree of skill of the practitioners in this art means that the specification needed to provide a correspondingly lower amount of guidance to enable them to practice the invention as claimed.

Finally, the rejection states that "the efficacy of said compounds in increasing erythropoietin mentioned above cannot be predicted . . . but must be determined from the case to case by painstaking experimental study." Action, at page 8. Since the instant application relates to reducing blood pressure rather than to increasing erythropoietin levels, it is clear that the enablement rejection in this case was imported into to the present Action from an unrelated case with a different specification. While the rejection therefore may represent an appropriate evaluation of the *Wands* factors to the claims under examination in whatever case it relates to, it does not represent an appropriate evaluation of those factors in this case. Applicants respectfully submit that when the *Wands* factors are applied and correctly weighted in view of the teachings of the present specification, the claims under examination are fully enabled.

**D. Rejection of the Claims as anticipated by Ichihara**

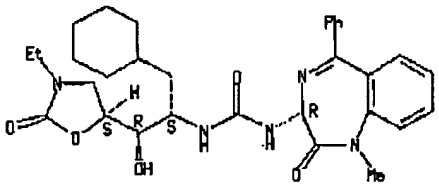
Claims 14-18, 21, 22, 30-34, 37, and 38 are rejected under §102(b) as anticipated by Ichihara, JP 07304755. According to the Action, Ichihara teaches compounds within the scope of the present Formula 1 for treatment of, among other things, hypertension. The Action states that the property of inhibiting sEH is deemed to be inherent in the compounds disclosed by Ichihara. Applicants respectfully rebut the rejection, as set forth below.

Applicants respectfully call the Examiner's attention to the accompanying Declaration of Dr. Bruce D. Hammock. Dr. Hammock, a co-inventor of the current application, holds the position of Distinguished Professor at the University of California at Davis and was elected to membership in the National Academy of Sciences in 1999. As attested to in the Declaration, he is also an author or co-author of over 600 articles in the scientific literature, of which well over 200 relate to the study of epoxide hydrolases, their activity, and the effects on inhibiting them. He further states that many of his recent publications have focused in particular

on studying the activity of the enzyme soluble epoxide hydrolase ("sEH") and the effects of inhibiting the ability of sEH to hydrolyse epoxides.

While the Examiner is respectfully requested to carefully review the entirety of the Declaration, the Examiner's attention is specifically directed to the following. Dr. Hammock states that his laboratory has now studied the structure activity relationship ("SAR") of over 2000 compounds (Declaration, at ¶ 6), and has crystal structures of both the murine and the human sEH enzyme bound to selected inhibitors. *Id.* He further declares that, as a result of these studies, he can now predict with a high degree of confidence what urea-based compounds will inhibit human sEH and which will not. *Id.*

Dr. Hammock was provided with the structures of each of the compounds from the Ichihara reference cited by the Action as taught by the reference for the treatment of cardiovascular disease. Based on the extensive SAR studies mentioned above, Dr. Hammock is able to state that the compounds cited would be inactive to poor inhibitors of sEH at physiologically relevant concentrations. (He notes that he puts in this qualification since many otherwise inactive compounds are capable of inhibiting an enzyme's activity if present at concentrations beyond those that can be achieved *in vivo*.) With regard to the first compound cited, RN 174398-90-4,

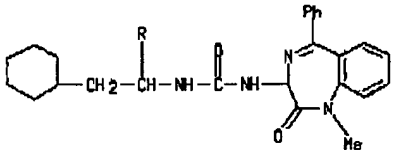


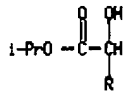

Dr. Hammock states:

> On the left side of the urea, the R group is too big and there is a polar group too close to the NH of the urea. The group to the right of the urea also has polar residues too close to the urea. Even with a highly potent group on the right side of the urea, the group on the left side would preclude activity. The crystal structure of the sEH enzyme shows a very hydrophobic catalytic tunnel except

> for very specific locations. Accordingly, I predict that this compound would be inactive as an inhibitor of sEH.

Declaration at ¶ 10, Part A. Similarly, with respect to the second compound cited, RN 174398-91-5,




Dr. Hammock states:

> The group to the right side of the urea is too bulky and the R groups on both sides of the urea have polar groups too close to the urea. Accordingly, I predict that this compound would be inactive as an inhibitor of sEH.

Declaration, at ¶ 10, Part B. Dr. Hammock also predicts that the other two compounds disclosed by Ichihara and cited by the Action as anticipating the invention likewise contain groups that are too bulky or polar to permit them to inhibit the enzyme. See, Declaration, at ¶ 10, Parts C and D.

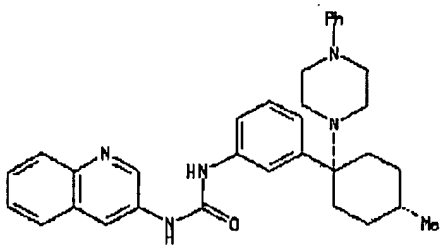
Dr. Hammock also comments on the compounds not expressly cited but that are set forth in a 2 page table at the end of the Ichihara reference. Dr. Hammock notes that, according to the structure on page 735, almost all have a 7-membered, heterocyclic ring with a substituted carbon next to the L1 substituent. Declaration, at ¶11. He states that these compounds will be inactive as sEH inhibitors because the 7-membered unsaturated ring will not fit into the active site of the enzyme. Declaration, at ¶11. He also notes that one compound on the table does not fall within Formula I. *Id.*

The rejection is based on an incorrect premise. Neither the compounds identified by the Action nor the other compounds disclosed in Ichihara but not specifically commented on by the Action would be active as sEH inhibitors at physiologically relevant concentrations. Accordingly, the rejection should be reconsidered and, Applicants submit, withdrawn.

**E. Rejection of the claims as anticipated by Blum**

Claims 14-18, 21-23, 27-34, and 37-40 are rejected under §102(e) as anticipated by Blum, U.S. Patent No. 5,962,455 (hereafter "Blum"). According to the Action, Blum teaches compounds within the scope of the present Formula 1 for treatment of, among other things, hypertension. The Action states that the property of inhibiting sEH is deemed to be inherent in the compounds disclosed by Blum and that the reference therefore anticipates the invention. Applicants respectfully rebut the rejection, as set forth below.

Dr. Hammock was provided with the structures of each of the compounds from the Blum reference cited by the Action as taught by the reference. Based on the extensive SAR studies of some 2000 compounds mentioned above, Dr. Hammock predicts that the compounds cited would be inactive as inhibitors of sEH at physiologically relevant concentrations. See, Declaration, at ¶12. With regard to the first compound cited, RN 202472-67-1,

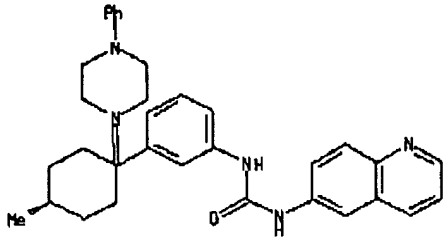



• 3 HCl

Dr. Hammock states:

> There is a slight chance the group on the left of the urea would yield activity with the correct substituents on the other side. However, the activity should be mediocre to poor. The group on the right is too large. I predict as well that the heterocycle will be far too polar. Accordingly, I predict that this compound would have poor to no activity as an inhibitor of sEH.

Declaration, at ¶ 12, Part A. Similarly, for the second compound, RN 204272-68-2,



• 3 HCl

Dr. Hammock states:

> This compound is similar to the one discussed [the compound of RN 204272-67-1] above, except that the sides are reversed. For the same reasons as set forth with respect to the preceding compound, I predict that this compound would have poor to no activity as an inhibitor of sEH.

Declaration, at ¶ 12, Part B. Dr. Hammock also predicts that the other two compounds disclosed by Blum and cited by the Action as anticipating the invention likewise contain groups that are too bulky or polar to permit them to inhibit the enzyme. See, Declaration, at ¶ 12, Parts C and D.

With respect to the other compounds disclosed in Blum but not specifically identified by the Action, Dr. Hammock notes that a polar group closer to the urea carbonyl than about 6 angstroms will eliminate the compounds from having activity as an inhibitor of sEH, and that this precludes many of the Blum compounds from having activity as inhibitors of sEH. Declaration, at ¶13. He further notes that many of the compounds listed in the general structures have R and R' groups on the 1 and 3 positions of the urea that will not confer activity. *Id.* Additionally, he notes that the majority of the general structures disclosed in Blum have very large and branched chain groups close to the urea which would dramatically reduce affinity for the enzyme. *Id.* He states that none of them have structures that would lead him to expect that they would inhibit sEH at physiologically relevant concentrations. *Id.* Finally, he notes that these compounds were designed to bind to the neuropeptide Y1 receptor, which of course has its own very specific properties, and that one would be very surprised if a similar structure activity relationship was observed between a peptide receptor and an enzyme dealing with highly lipophilic fatty acid oxides. *Id.*

The rejection is based on an incorrect premise. Neither the compounds identified by the Action as disclosed by Blum and expressly or inherently reading on the claims as presented nor the other compounds disclosed in Blum but not specifically commented on by the Action would be active as sEH inhibitors in physiologically relevant concentrations. The person of skill would recognize that such poor inhibitors would have to be administered in such large amounts that they would not be therapeutically useful agents. Accordingly, the rejection should be reconsidered and, Applicants submit, withdrawn

**F. Rejection of the claims as obvious over Blum in view of the Merck Manual**

Claims 26 and 41 are rejected under §103(a) as obvious over Blum, above, and further in view of the Merck Manual (15th Ed. 1987). According to the Action, Blum teaches compounds within the scope of Formula I which inherently have the property of reducing blood pressure and cites the Merck Manual merely for these claims, which recite reduction of systolic blood pressure, which is not specifically mentioned in Blum. Applicants rebut in part and traverse the rejection.

As noted in the preceding section, none of the compounds disclosed by Blum, whether expressly cited by the Action or otherwise described in the reference, are predicted to inhibit the epoxide hydrolase activity of sEH at physiologically active concentrations. Accordingly, Blum does not teach, alone or in combination with the Merck Manual, compounds which read on claims 26 and 41. Reconsideration and withdrawal of the rejection are respectfully requested.

**G. Rejections for Double Patenting**

**1. Rejection of claims 30-34**

Claims 30-34 are rejected under §101 as claiming the same invention as that of claims 1-5 of U.S. Patent No. 6,531,506 (hereafter, the "'506 patent'"). The Action notes that a rejection under §101 can be overcome by amending the claims so they are not coextensive in scope with the claims with which they are alleged to be the same. To expedite prosecution,

claim 30 has been amended to include a recitation that the inhibitor of sEH inhibits activity of the enzyme by 50 % at a concentration of less than about 500 micromolar (that is, that it has an $IC_{50}$ of less than about 500 micromolar). Applicants respectfully request reconsideration and withdrawal of the rejection in view of the amendment.

**2. Rejection of claims 14-18, 21-23, 26-34, and 37-41**

Claims 14-18, 21-23, 26-34, and 37-41 are rejected for obvious type double patenting over claims 6-9 of the '506 patent. According to the Action, while the claims are not identical, they are not patentably distinct because both the application and the '506 patent are directed to therapeutic treatment of hypertension with the same compounds. To expedite prosecution, claim 14 has been amended to include a recitation that the inhibitor of sEH inhibits activity of the enzyme by 50 % at a concentration of less than about 500 micromolar (that is, that it has an $IC_{50}$ of less than about 500 micromolar). Applicants respectfully request reconsideration and withdrawal of the rejection in view of the amendment.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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